## Remarks

Upon entry of this Amendment, claims 1, 8, 10 to 25, and 29 will be pending. No claims are added. Claims 1, 8, 10 to 13, 18 to 25, and 29 are amended. Support for the claim amendments may be found through out the specification as filed. *See, for example*, page 4, lines 1 to 9 and 15 to 21; and page 47, lines 7 to 8. Therefore, no new matter is introduced.

Applicants respectfully request reconsideration and allowance of the present application.

*Information Disclosure Statement (IDS):*

The Examiner did not consider the following reference, which Applicants submitted with the IDS filed on July 13, 2006, because it was not in English:

González-Ordóñez, "Bases Genéticas de la Enfermedad Tromboembólica Venosa," *Química Clinica* **22**, 367-381 (2003).

Applicants respectfully submit that they included an English language abstract of this reference, *which was part of the González-Ordóñez reference* (see the section in the middle of p. 367, which is the first page of the González-Ordóñez reference). For the convenience of the U.S. Patent and Trademark Office, Applicants submit another IDS and PTO Form-1449, and another copy of González-Ordóñez, which as noted previously includes a copy of the English language abstract. Applicants respectfully request that the Examiner initial and return the PTO Form-1449 to the Applicants.

*Election/Restrictions:*

In the response to the Election/Restriction Requirement dated August 16, 2007, Applicants elected, *inter alia*, the 143 mutations or polymorphisms listed in Table 1. In the response, Applicants also amended the claims to reflect this election. The present Office Action states, however, that claim 1 and the dependent claims "are not commensurate in scope with the election of the 143 mutations or polymorphisms in Table 1." Therefore, the claims were examined to include the limitation "wherein the presence of all 143 mutations or polymorphisms indicates (*sic*) that the subject has a genetic predisposition to VT." (emphasis added).

Applicants respectfully disagree with the Office's understanding of the Applicants election of the 143 mutations or polymorphisms listed in Table 1 and the statement that the claims are not commensurate in scope with this election. For example in claim 1, the claimed method comprises screening a human subject for all of the 143 mutations or polymorphisms listed in Table 1, wherein if the subject has one or more of the 143 mutations or polymorphisms listed in Table 1, the subject has a predisposition for VT. Claim 1 is amended to more clearly describe this scope. Accordingly, Applicants respectfully request that the Office examine the entire scope of the claims.

*Objections to the claims:*

Claims 23 to 25 were objected to because they do not properly depend from claim 1. Applicants respectfully request reconsideration. This objection is moot as a result of the amendments to claims 23 to 25, which now are directed to a method of selecting a VT therapy, comprising, *inter alia*, detecting a genetic predisposition to VT.

Claim 29 was objected to because it does not properly depend from claim 13. Applicants respectfully request reconsideration. This objection is moot as a result of the amendment to claim 29, which is now directed to a method of detecting a genetic predisposition to VT, comprising, *inter alia*, applying amplification products of claim 13 to an array.

In conclusion, Applicants respectfully request reconsideration and withdrawal of the objections to claims 23 to 25 and 29.

*Rejections under 35 U.S.C. § 112, second paragraph:*

Claims 1, 8, 10 to 25, and 29 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants respectfully request reconsideration and submit that this rejection is moot as a result of the amendments to claims 1, 8, 10 to 25, and 29. For example, the independent claims are amended to remove the "at least" phrase and to remove other unnecessary language which clarifies the claims. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*Rejections under 35 U.S.C. § 112, first paragraph:*

Claims 1, 8, 10 to 25, and 29 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully disagree and traverse this rejection using the categories set forth in the Office Action.

The breadth of the claims and the nature of the invention –

Claims 1, 8, 10 to 25, and 29 are amended to, *inter alia*, human subjects.

Guidance in the specification and working examples –

Applicants respectfully submit that the Office has misunderstood the teachings of the specification and the working examples provided. For example, the Office Action states that:

- Table 3 "does not teach which Antithrombin III polymorphism was analyzed to yield the data in the table";
- "it is unclear from the data in the specification how to use each of the 10 analyzed polymorphisms/mutations to determine genetic predisposition to venous thrombosis in any population";
- "many of the likelihood ratios were only calculated for certain ethnic populations: for example, the fibrinogen Thr312A1a polymorphism was only analyzed in Caucasian populations;" and
- "since there is no data in the specification for the remaining 133 polymorphisms it is unpredictable to use any of the 133 polymorphisms/mutations to determine genetic predisposition to venous thrombosis in any population."

What Table 3 shows is that if, for example, any Antithrombin III a polymorphism/ mutation associated with VT is found, there is a 1.6% probability of developing VT. Probability data for specific polymorphisms/mutations are shown for certain genes and not others but the relevant inquiry is not whether certain gene/polymorphism/mutation/population is shown in Table 3 or not. Rather, Table 3 clearly shows that instead of analyzing individual genes, polymorphisms, mutations, or populations, the use of all eight genes permits one to determine a subject's genetic predisposition of developing VT with a much higher probability (*e.g.*, 1.6% vs. 85.1% to 99.7%). This probability is at least 98% in Caucasians, at least 85% in Asians, and at least 87% in Africans.

Unpredictability of the art, state of the prior art, level of skill in the art –

The Office Action lists three articles (Nagaraja *et al.*, *J. Clin. Neurosci.* **14(7)**, 635-638 (2007); Bezemer *et al.*, *Arch. Intern. Med.* **167(5)**, 497-501 (2007); and Halushka *et al.*, *Nat. Genet.* **22**, 239-247 (1999)) apparently to show that individual genes cannot accurately be associated with VT. The Office uses three more articles (Hirschhorn *et al.*, *Genet. Med.* **4(2)**, 45-61 (2002); Ioannidis, *Nat. Genet.* **29**, 306-309 (2001); and Kroese *et al.*, *Genet. Med.* **6**, 475-480 (2004)) apparently to reiterate that the correlation between individual polymorphisms and diagnoses of certain diseases may be inaccurate.

Applicants respectfully submit that notwithstanding the teachings of any, or all, the articles listed, the claims fully satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Indeed, it is because of the uncertainty regarding the use of *one* gene polymorphism or mutation to predict VT, that the pending claims provide for screening all 143 mutations or polymorphisms listed in Table 1, namely polymorphisms or mutations in antithrombin III (AT III), protein C, protein S, fibrinogen, factor V (FV), prothrombin (factor II), methylenetetrahydrofolate reductase (MTHFR) and angiotensin 1-converting enzyme (ACE). As the Office notes, the concurrent screening of the eight genes results in a probability of developing VT of at least 98% in Caucasians, at least 85% in Asians, and at least 87% in Africans. In other words, far from being uncertain or inaccurate, the presence of mutations or polymorphisms in at least these eight genes results in highly accurate and measurably certain probabilities.

Quantity of experimentation –

Applicants respectfully submit that, as argued previously, the specification provides sufficient quanta of experimentation to support the amended claims 1, 8, 10 to 25, and 29.

In conclusion, Applicants respectfully submit that, as amended, claims 1, 8, 10 to 25, and 29 are fully enabled by the specification as filed. Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

If there are any issues to be resolved before a Notice of Allowance is granted, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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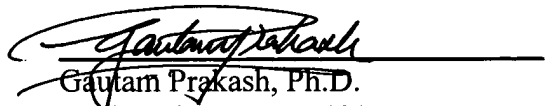

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